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Comparison of ketamin and medazolas in premedication in children

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Abstract
Fears of operation, injections, physicians and operation theatre environment where the children are separated from their parents prior to anesthesia produces traumatic experiences in the mind of the young children.
Patients and methods: ninety children of both sex, ASA physical status I-II, aged 4–7 years, scheduled for tonsillectomy operations. randomly allocated to 1 of the 3 groups 30 patients each by using a random number table.
Group M (Midazolam): Patients were premedicated with a dose of 0.5 mg/kg of injectable midazolam mixed in sugar free apple juice.
Group K (Ketamine): Patients were premedicated with a dose of (5 mg/kg) mixed in sugar free apple juice in total solution of 0.5 ml/kg.
Group C (Clonidine): Patients were premedicated with a dose of (4 mcg/kg).
The Clonidine was prepared by dissolving crushed tablets of Clonidine. Oral sedative premedication in the form of syrup will be given 45 min before induction of general anesthesia, in the presence of parent.on arrival to the OR assessment of sedation score, easy separation score and behavior at time of venipuncture after induction of anesthesia recovery was assessed as base line then postoperative every 5 min till baseline score regained, using "Vancouver sedative recovery scale for children". The incidences of adverse effects were also recorded. Then Assessment of amnesia after 24 hours by a telephone recall questionnaire of the parents.
Results: Sedation score was statistically significant difference among the groups after sedation from before sedation with no statistically significant difference among the studied groups (P = 0.108). Ease of separation scores was statistically significant difference among the groups after sedation from before sedation and there were statistically significant difference between ketamine and clonidine groups (P = 0.036) after sedation.
As regard behavior at time of venipuncture scale among the three groups shows that ketamine administration resulted in better behavior than midazolam administration (P = 0.008), and clonidine administration (P = 0.004).As regard recovery and discharge times from anesthesia it was most rapid for group M and slowest for group K. The variation in recovery time between both groups M and K and groups M and C were very highly significant.
Conclusion: Oral administrations of ketamine 5 mg /kg is a suitable alternative to oral midazolam and provide better sedation than oral midazolam or oral clonidine but it slow in recovery when used as a sedative premedication in children.

Keywords: midazolam, ketamine, clonidine, sedation

1. Introduction
Children undergoing stress during induction of anesthesia have postoperative maladaptive behaviors which could be decreased through the use of appropriate sedation. [1, 2]. Benzodiazepines are the most commonly used premedication agents in children. They produce anxiolysis, sedation, and amnesia and reduce PONV [3]. Despite their efficacy in the treatment of emergence agitation, midazolam premedication has not been reported to prevent it. Impaired post-operative cognitive function has been reported after midazolam premedication in children [4]. Ketamine has been investigated as an alternative premedication [5, 6]. The IV preparation of Ketamine can be mixed with cola or fruit syrup to create an oral mixture of Ketamine, which is favorably accepted by most children [6]. The time of onset of the action of orally administered Ketamine is also dose related with large-dose orally administered Ketamine (6 mg/kg) having an onset of action of 10 min and small-dose Ketamine leading to sedation within 20 min [5,7] Clonidine has significant sedative and analgesic properties because of its alpha-2 adrenergic agonism. Also it produces pre-operative sedation and anxiolysis in children and can be administered orally (4 mcg/kg) and intranasally (2mcg/kg) [8].

2. Methods
After obtaining the local ethics committee's approval, we obtained informed written consent from the children's parents. We studied 90 child of both sex, ASA physical status I-II, aged 4–7 years, and who were scheduled to undergoing Tonsillectomy in El-Hussein University hospital. The exclusion criteria included: children with a history of chronic illness, gastrointestinal tract disorders or malformation, known reactions to the drugs used, seizure disorder, and an active or recent upper respiratory tract infection.
Children were kept fasting for 6 hours for solid food and 2 hours for clear fluids. By using a sealed envelope technique, (Random permuted blocks) the patients were allocated randomly into three groups; 30 patients in each. Group M (Midazolam): patients were pre-medicated with a dose of (0.5 mg/kg) [9] of injectable midazolam, (Dormicum, Roche, ampule contain 15 mg/3ml mixed in sugar free apple juice limiting the total volume mixed with a double volume of apple juice).
Group K (Ketamine): Patients were premedicated with a dose of (5 mg/kg) [10]. 5 mg/kg by 5 % Ketamine (Ketalar ®, Pfizer, 50 mg/ml in 10 ml vial) mixed in sugar free apple juice in total solution of 0.5 ml/kg. [10]Group C (Clonidine): Patients were

premedicated with a dose of (4 mcg/kg). [11] 4 mcg/kg by Clonidine tablets (Catapress®, Boehringer Ingelheim, 150 mcg). The Clonidine was prepared by dissolving crushed tablets of Clonidine in 10 ml of 5% dextrose [12].

In the pre-operative holding area and in the presence of the child parent, oral premedication in the form of syrup were given 45 minutes before induction of general anesthesia. Children who refused to take the whole dose were excluded from the study. On arrival at the OR, the level of sedation was assessed by 3- point sedation score [13] was used to assess sedation at the time of administration of the pre-medication (baseline) and reassessed again after 45 minutes of its administration.

The scores were Excellent (Fully cooperative, unafraid, or asleep); Good (Mild to moderate fear and/or crying which ceases and child becomes cooperative with reassurance); and Poor (Uncooperative, crying, inconsolable).

Ease of Separation score [14] was used to assess the children's responses when taken away from the parents at the time of administration of the pre-medication (base line) and reassessed again after 45 minutes of its administration and graded them as Excellent (Patient unafraid, cooperative or asleep); Good (Slight fear and/or crying, quiet with reassurance); fair (Moderate fear and crying, not quiet with reassurance); or poor (Crying, need for restraint) baseline reading then after 45 min.

Behavior at time of venipuncture scale [7] Used to evaluate the behavior of the child at time of puncture for putting intravenous line in the OR: (1- fight without success 2-fight with success 3-minor resistance 4- no reaction). Then, routine monitoring was connected before induction of anesthesia (heart rate, non-invasive arterial blood pressure, and peripheral oxygen saturation).

Anesthesia was induced by propofol 2 mg/kg IV, fentanyl 1µg/kg, inhalational 2% sevoflurane in oxygen. Then the endotracheal intubation was done, after administration of atracurium 0.5 mg/kg. Anesthesia was maintained with sevoflurane 1% in oxygen with controlled ventilation. During surgery children received lactated Ringer's solution 6 m/ kg/h, whereas, in the postoperative period, 5% dextrose in 0.45% NaCl was infused at 4 mL/kg/h.

We defined an intraoperative reduction of MAP or HR by >30% of baseline values as hypotension or bradycardia, respectively; as necessary, these were treated by fluid bolus, ephedrine, or atropine. Residual neuromuscular block was antagonized with atropine sulphate 0.02 mg/kg and neostigmine 0.05 mg/kg. After extubation, the patients were admitted to the post-anesthetic care unit for at least 2 hours until complete recovery. HR was monitored, as well as SpO2 and MAP.

The recovery time was recorded from discontinuation of anesthesia until the baseline score was regained; using "Vancouver sedative recovery scale for children" [15]. The baseline was assessed before giving sedation preoperatively then reassessed every 5 minute postoperatively until the base line score was regained. The discharge time was recorded from discontinuation of anesthesia until achievement of a score of 10-12 of "The Short-Stay Surgery Discharge Score"[16] which was evaluated postoperatively every 30 minute until discharge.

Anterograde amnesia was assessed after 24 h by means of a telephone call to the parents; the conversation included questions pertaining to recall of the events that took place after the administration of sedation. The quality of anterograde amnesia was rated as 'yes'or 'no' [17]. The incidence of adverse effects such as nausea; vomiting; laryngospasm in the pre-induction area; postoperative agitation; and pre-operative hiccough were recorded.

2.2 Statistical analysis of the data

The sample size was calculated using the Medcalt program, version 3.2. The minimum sample size was 25 in each group and the present study included 30 in each group, with type I error (a) 0.05 and type II error (β) 0.01 by power of test 90%. We fed the data into a computer and analyzed it using SPSS software package (version 20.0; IBM). Qualitative data were described using numbers and percentages and quantitative data using mean and SD for normally distributed data. Using the c2-test, we tested and made comparisons of categorical variables between the different groups.

When more than 20% of the cells had an expected count less than 5,a correction for c2 by using Fisher's exact test or Monte Carlo correction was made. The distributions of quantitative variables for normality were tested using the Kolmogorov–Smirnov test, the Shapiro–Wilk test, and the D'Agstino test. Histograms and QQ plots for vision were also used.

Parametric tests were applied for normally distributed data: the F-test (ANOVA) was used to analyze for comparisons between the studied groups; in addition, we used the post-hoc test (Scheffe, which was assessed using adjusted Bonferroni and ANOVA with repeated measures to make comparisons between different periods).

Nonparametric tests were used for abnormally distributed data: the Kruskal–Wallis test was used to make comparisons between groups and the Mann–Whitney test to conduct a pair wise comparison. Also, the Wilcoxon signed-rank test was applied to make comparisons between the two stages. Significance of test results was quoted as two tailed probabilities. The significance of the obtained results was judged at the 5% level. P value of 0.05 or less was considered significant.

3. Results

This study conducted on 90 children of both sex undergoing tonsillectomy operation. The three Groups (M, K and C) were comparable with respect to patient age,sex, body weight and duration of surgery.

Table 1: Comparison between the studied groups according to demographic data

	Midazolam (n = 30)	Ketamine (n = 30)	Clonidine (n = 30)	P
Age (years)	4.89±0.77	4.79±0.92	5.11±0.86	0.329
Sex (M/F)	17/13	20/10	19/11	0.718
Weight (Kg)	17.93±2.20	17.23±2.18	17.67 ± 1.90	0.430
Duration of surgery (min)	38.67±12.99	39.17±12.04	39.17±12.39	0.984

There was no statistically significant difference in sedation scores among the groups prior to administration of sedation. However, sedation scores in the three groups differed significantly after sedation (at 45 minutes after drug administration) from before sedation.

Table 2: Comparison between the studied groups according to sedation score

	Midazolam (n = 30)	Ketamine (n = 30)	Clonidine (n = 30)	p_1
Before sedation				
Poor	22 (73.3%)	23 (76.7%)	23 (76.7%)	
Good	7 (23.3%)	7 (23.3%)	7 (23.3%)	0.914
Excellent	1 (3.3%)	0 (0.0%)	0 (0.0%)	
After sedation				
Poor	0 (0.0%)	0 (0.0%)	4 (13.3%)	
Good	7 (23.3%)	6 (20.0%)	8 (26.7%)	0.108
Excellent	23 (76.7%)	24 (80.0%)	18 (60.0%)	
p_2	<0.001***	<0.001***	<0.001***	

Data expressed as absolute value of patients number and % of total. P1:Sig.between studied groups P2; Sig.between before and after premedication * Significant ** highly significance, *** Very highly significance

3.1 Ease of separation scores

There was no statistically significant difference in ease of separation score scores among the groups prior to administration of sedation (P = 0.947). However, ease of separation scores in the three groups differed significantly after sedation (at 45 minutes after drug administration) from before sedation.

With no statistically significant among the three studied groups (P = 0.093) and there were statistically significant difference between ketamine and clonidine groups (P = 0.036) after sedation (at 45 minutes after drug administration).

Table 3: Comparison between the studied groups according to ease of separation score

	Midazolam (n = 30)	Ketamine (n = 30)	Clonidine (n = 30)	p_1
Before sedation				
Poor	22 (73.3%)	23 (76.7%)	23 (76.7%)	
Fair	4 (13.3%)	4 (13.3%)	4 (13.3%)	0.947
Good	3 (10.0%)	3 (10.0%)	3 (10.0%)	
Excellent	1 (3.3%)	0 (0.0%)	0 (0.0%)	
After sedation	Sig. bet. K-C*			
Poor	1 (3.3%)	0 (0.0%)	5 (16.7%)	
Fair	1 (3.3%)	1 (3.3%)	2 (6.7%)	0.093
Good	8 (26.7%)	6 (20.0%)	7 (23.3%)	
Excellent	20 (66.7%)	23 (76.7%)	16 (53.3%)	
p_2	<0.001***	<0.001***	<0.001***	

Data expressed as absolute value of patients number and % of total. P1:Sig.between studied groups P2; Sig.between before and after premedication * significant ** highly significance, *** Very highly significance

3.2 Behavior at time of venipuncture scale

Behavior at time of venipuncture scales among the three groups differed significantly at time of cannulation [45 minutes after drug administration] (P = 0.008). At this time, ketamine administration resulted in better behavior than midazolam administration (P = 0.008), and clonidine administration (P = 0.004).with no significant difference between midazolam and clonidine groups (P = 0.896).

Table 4: Comparison between the studied groups according to behavior at time of venipuncture scale

	Midazolam (n=30)	Ketamine (n=30)	Clonidine (n=30)	P
Behavior at time of venipuncture scale	Sig. bet. M-K**, K-C**			
Fight without success	4 (13.3%)	2 (6.7%)	4 (13.3%)	
Fight with successes	9 (30.0%)	1 (3.3%)	9 (30.0%)	0.008**
Minor resistance	6 (20.0%)	7 (23.3%)	7 (23.3%)	
No reaction	11 (36.7%)	20 (66.7%)	10 (33.3%)	

Data expressed as absolute value of patients number and % of total * significant ** highly significance, *** Very highly significance

3.3 Recovery and discharge times

The recovery time from anesthesia was most rapid for group M and slowest for group K. The variation in recovery time between both groups M and K and groups M and C were very highly significant ($P< 0.001$), with no significant difference between K and C groups. However, there was no difference in discharge times to home among the groups.

Table 5: Comparison between the studied groups according to recovery and discharge times

	Midazolam (n=30)	Ketamine (n=30)	Clonidine (n=30)	P
Recovery time	15.3 ± 5.2	22.8 ± 5.0[a]	21.2 ± 4.7[a]	<0.001***
Discharge time	171.0 ± 31.7	186.0 ± 32.9	178.0 ± 24.8	0.159

Data was presented as Mean ± SD. for normally distributed data * significant ** highly significance, *** Very highly significance
a: significant with midazolam group

3.4 Anterograde amnesia

Anterograde amnesia was much pronounced for patients of group M in comparison to groups K and C. The variation in achievement of amnesia between both groups M and C and groups K and C were very highly significant.

Table 6: Comparison between the studied groups according to achievement of amnesia

	Midazolam (n=30)	Ketamine (n=30)	Clonidine (n=30)	P
Achievement of amnesia	Sig. bet. M-C***, K-C***			
	22 (73.3%)	21 (70.0%)	7 (23.3%)	<0.001***

Data expressed as absolute value of patients number and % of total. * Significant ** highly significance, *** Very highly significance.

3.5 Adverse effects

Incidence of adverse effects was statistically significantly different between the three studied groups, with very highly significant difference between group K and group C and no significant difference between both groups M and K and groups M and C. Incidence of PONV and postoperative agitation was much pronounced for patients of group K, with only three patient had hiccough and one patient suffered desaturation in the preoperative period in group M and one patient suffered laryngeospasm in the preoperative holding area in ketamine group.

Table 7: Comparison between the studied groups according to incidence of adverse effects

	Midazolam (n=30)	Ketamine (n=30)	Clonidine (n=30)	P
AE	Sig. bet. K-C***			
No	16 (53.3%)	13 (43.3%)	27 (90.0%)	0.001*
PONV	4 (13.3%)	8 (26.7%)	2 (6.7%)	
Agitation	6 (20.0%)	7 (23.3%)	1 (3.3%)	
Hiccough	3 (10.0%)	0 (0.0%)	0 (0.0%)	
Desaturation	1 (3.3%)	0 (0.0%)	0 (0.0%)	
Laryngeospasm	0 (0.0%)	2 (6.7%)	0 (0.0%)	

* significant ** highly significance, *** Very highly significance

4. Discussion

Orally acceptable premedication in children can overcome problems of forceful separation from parents prior to anaesthesia with stormy induction with painful canulation. The drugs selected in the present study aimed at achieving a state of conscious sedation. It reduces the fear of pain and anxiety associated with parental separation [18].

Several doses [19, 20] of midazolam have been tried for adequate preoperative sedation and anxiolysis in children. The dose of midazolam chosen for this study (0.5 mg/Kg) reflects common clinical practice. Moreover, such dose used in the current study may avoid side effects before the induction of anesthesia described with higher doses in other studies [21, 22]. While other studies [23] tried lower doses of oral midazolam. As regard Sedation score and Ease of separation scores; The result of the present study in accordance with the result done by Turhanoilu *et al.* [24] who found that adequate sedation was observed for 80% of patients received 8 mg/kg ketamine and for 45% in patients received 6 mg/kg ketamine and in none of the patients received 4 mg/kg ketamine after 10 min from drinking the mixture.

Thirty minutes after the premedication sedation was significantly more profound in all treatment groups than in control group and the baseline values of the groups and also they found that 95% of children received 8 mg/kg ketamine were calm at the moment of separation from their parents and showed minor reaction when the intravenous catheter was inserted just before induction of anaesthesia.

Tazeroualti *et al*. [25] who studied the effect of oral premedication with midazolam 0.5mg/kg, clonidine 2 mcg/kg, and clonidine 4 mcg/kg by 30 minute before anesthesia and they found that quality of induction was estimated to be good in 70% of the children in the midazolam group, compared with 50% in the clonidine 2 mcg/kg group and 30% in the clonidine 4 mcg/kg group.

Trevor *et al*. [26] compared oral premedication with midazolam 0.5 mg/kg versus clonidine 4ug/kg and he found that the percentage of children who were sedated and calm increased in both the groups. The overall level of sedation was better in the children in the clonidine group, but children in the midazolam group had a greater degree of anxiolysis at times of venipuncture and mask application so they concluded that oral midazolam is superior to clonidine as an anxiolytic in pediatric population.

5. Conclusion

Oral administrations of ketamine 5 mg /kg is a suitable alternative to oral midazolam and provide better sedation than oral midazolam or oral clonidine but it slow in recovery when used as a sedative premedication in children.

6. References

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